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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification : A61N 1/362	AI	(11) International Publication Number: WO 00/01443 (43) International Publication Date: 15 January 2000 (1901.00)
(21) International Application Number: PCT/US98/13737 (22) International Filing Date: 2 July 1998 (02.07.98) (71/72) Applicant and Inventor: MOWER, Morton, M. [US/US]; 3908 North Charles Street #1001, Baltimore, MD 21218 (US). (74) Agent: ROBERTS, Jon, L.; Roberts & Abokhair, LLC, Suite 1000, 11800 Sunrise Valley Drive, Reston, VA 20191-5302 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MH, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, ME, NE, SN, TD, TG). Published With international search report.	

(54) Title: AUGMENTATION OF ELECTRICAL CONDUCTION AND CONTRACTILITY BY BIPHASIC CARDIAC PACING

(57) Abstract

A first stimulation phase is administered to the muscle tissue. The first stimulation phase has a predefined polarity, amplitude and duration. A second stimulation phase is then administered to the muscle tissue. This second phase also has a predefined polarity, amplitude and duration. The two phases are applied sequentially. Contrary to current thought, anodal stimulation is first applied, followed by cathodal stimulation. In this fashion, pulse conduction through the cardiac muscle is improved together with an increase in contractility. The technique can also be applied to large muscle tissue stimulation other than cardiac muscle.

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AUGMENTATION OF ELECTRICAL CONDUCTION AND CONTRACTILITY BY BIPHASIC CARDIAC PACING

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FIELD OF THE INVENTION

This invention relates generally to a method for the stimulation of muscle tissue. In particular, this invention relates to a method for cardiac stimulation and pacing with biphasic waveforms leading to improved conduction and contractility.

BACKGROUND OF THE INVENTION

The function of the cardiovascular system is vital for survival. Through blood circulation, body tissues obtain necessary nutrients and oxygen, and discard waste substances. In the absence of circulation, cells begin to undergo irreversible changes that lead to death. The muscular contractions of the heart are the driving force behind circulation.

In cardiac muscle, the muscle fibers are interconnected in branching networks that spread in all directions through the heart. When any portion of this net is stimulated, a depolarization wave passes to all of its parts and the entire structure contracts as a unit. Before a muscle fiber can be stimulated to contract, its membrane must be polarized. A muscle fiber generally remains polarized until it is stimulated by some change in its environment. A membrane can be stimulated electrically, chemically, mechanically or by temperature change. The minimal stimulation strength needed to elicit a contraction is known as the threshold stimulus. The maximum stimulation amplitude that may be administered without eliciting a contraction is the maximum subthreshold amplitude.

Where the membrane is stimulated electrically, the impulse amplitude required to elicit a response is dependent upon a number of factors. First, is the duration of current flow. Since the total charge transferred is equal to the current amplitude times the pulse duration, increased stimulus duration is associated with a decrease in threshold current amplitude. Second, the percentage of applied current that actually traverses the membrane varies inversely with electrode size. Third, the percentage of applied current that actually traverses the membrane varies directly with the proximity of the electrode to the tissue. Fourth, the impulse amplitude required to elicit a response is dependent upon the timing of stimulation within the excitability cycle.

Throughout much of the heart are clumps and strands of specialized cardiac muscle tissue. This tissue comprises the cardiac conduction system and serves to initiate and distribute

1 depolarization waves throughout the myocardium. Any interference or block in cardiac impulse
2 conduction may cause an arrhythmia or marked change in the rate or rhythm of the heart

3 Sometimes a patient suffering from a conduction disorder can be helped by an artificial
4 pacemaker. Such a device contains a small battery powered electrical stimulator. When the
5 artificial pacemaker is installed, electrodes are generally threaded through veins into the right
6 ventricle, or into the right atrium and right ventricle, and the stimulator is planted beneath the
7 skin in the shoulder or abdomen. The leads are planted in intimate contact with the cardiac
8 tissue. The pacemaker then transmits rhythmic electrical impulses to the heart, and the
9 myocardium responds by contracting rhythmically. Implantable medical devices for the pacing
10 of the heart are well known in the art and have been used in humans since approximately the mid
11 1960s.

12 Either cathodal or anodal current may be used to stimulate the myocardium. However
13 anodal current is thought not to be useful clinically. Cathodal current comprises electrical pulses
14 of negative polarity. This type of current depolarizes the cell membrane by discharging the
15 membrane capacitor, and directly reduces the membrane potential toward threshold level.
16 Cathodal current, by directly reducing the resting membrane potential toward threshold has a
17 one-half to one-third lower threshold current in late diastole than does anodal current. Anodal
18 current comprises electrical pulses of positive polarity. The effect of anodal current is to
19 hyperpolarize the resting membrane. On sudden termination of the anodal pulse, the membrane
20 potential returns towards resting level, overshoots to threshold, and a propagated response occurs.
21 The use of anodal current to stimulate the myocardium is generally discouraged due to the higher
22 stimulation threshold, which leads to use of a higher current, resulting in a drain on the battery of
23 an implanted device and impaired longevity. Additionally, the use of anodal current for cardiac
24 stimulation is discouraged due to the suspicion that the anodal contribution to depolarization can,
25 particularly at higher voltages, contribute to arrhythmogenesis.

26 Virtually all artificial pacemaking is done using stimulating pulses of negative polarity, or
27 in the case of bipolar systems, the cathode is closer to the myocardium than is the anode. Where
28 the use of anodal current is disclosed, it is generally as a charge of minute magnitude used to
29 dissipate residual charge on the electrode. This does not affect or condition the myocardium
30 itself. Such a use is disclosed in U.S. Patent No. 4,543,956 to Herscovici.

31 The use of a triphasic waveform has been disclosed in U.S. Patent Nos. 4,903,700 and
32 4,821,724 to Whigham et al., and U.S. Patent No. 4,343,312 to Cals et al. Here, the first and

1 third phases have nothing to do with the myocardium per se, but are only envisioned to affect the
2 electrode surface itself. Thus, the charge applied in these phases is of very low amplitude.

3 Lastly, biphasic stimulation is disclosed in U.S. Patent No. 4,402,322 to Duggan. The
4 goal of this disclosure is to produce voltage doubling without the need for a large capacitor in the
5 output circuit. The phases of the biphasic stimulation disclosed are of equal magnitude and
6 duration.

7 Enhanced myocardial function is obtained through the biphasic pacing of the present
8 invention. The combination of cathodal with anodal pulses of either a stimulating or
9 conditioning nature, preserves the improved conduction and contractility of anodal pacing while
10 eliminating the drawback of increased stimulation threshold. The result is a depolarization wave
11 of increased propagation speed. This increased propagation speed results in superior cardiac
12 contraction leading to an improvement in blood flow. Improved stimulation at a lower voltage
13 level also results in reduction in power consumption and increased life for pacemaker batteries.

14 As with the cardiac muscle, striated muscle may also be stimulated electrically,
15 chemically, mechanically or by temperature change. Where the muscle fiber is stimulated by a
16 motor neuron, the neuron transmits an impulse which activates all of the muscle fibers within its
17 control, that is, those muscle fibers in its motor unit. Depolarization in one region of the
18 membrane stimulates adjacent regions to depolarize also, and a wave of depolarization travels
19 over the membrane in all directions away from the site of stimulation. Thus, when a motor
20 neuron transmits an impulse, all the muscle fibers in its motor unit are stimulated to contract
21 simultaneously. The minimum strength to elicit a contraction is called the threshold stimulus.
22 Once this level of stimulation has been met, the generally held belief is that increasing the level
23 will not increase the contraction. Additionally, since the muscle fibers within each muscle are
24 organized into motor units, and each motor unit is controlled by a single motor neuron, all of the
25 muscle fibers in a motor unit are stimulated at the same time. However, the whole muscle is
26 controlled by many different motor units that respond to different stimulation thresholds. Thus,
27 when a given stimulus is applied to a muscle, some motor units may respond while others do not.

28 The combination of cathodal and anodal pulses of the present invention also provides
29 improved muscular contraction where electrical muscular stimulation is indicated due to neural
30 or muscular damage. Where nerve fibers have been damaged due to trauma or disease, muscle
31 fibers in the regions supplied by the damaged nerve fiber tend to undergo atrophy and waste
32 away. A muscle that cannot be exercised may decrease to half of its usual size in a few months.
33 Where there is no stimulation, not only will the muscle fibers decrease in size, but they will

1 become fragmented and degenerated, and replaced by connective tissue. Through electrical
2 stimulation one may maintain muscle tone, such that upon healing or regeneration of the nerve
3 fiber, viable muscle tissue remains.

4 Where muscle tissue has been damaged due to injury or disease, the regenerative process
5 may be assisted by electrical stimulation. Enhanced muscle contraction is obtained through the
6 biphasic stimulation of the present invention. The combination of cathodal with anodal pulses of
7 either a stimulating or conditioning nature results in contraction of a greater number of motor
8 units at a lower voltage level, leading to superior muscle response.

9 SUMMARY OF THE INVENTION

10 It is therefore an object of the present invention to provide improved stimulation of
11 cardiac tissue.

12 It is another object of the present invention to increase cardiac output through superior
13 cardiac contraction leading to greater stroke volume.

14 It is another object of the present invention to increase impulse propagation speed.

15 It is another object of the present invention to extend pacemaker battery life.

16 It is a further object of the present invention to obtain effective cardiac stimulation at a
17 lower voltage level.

18 It is a further object of the present invention to eliminate the necessity of placing
19 electrical leads in intimate contact with tissue to obtain tissue stimulation.

20 It is a further object of the present invention to provide improved stimulation of muscle
21 tissue.

22 It is a further object of the present invention to provide contraction of a greater number of
23 muscle motor units at a lower voltage level.

24 A method and apparatus for muscular stimulation in accordance with the present
25 invention includes the administration of biphasic stimulation to the muscle tissue, wherein both
26 cathodal and anodal pulses are administered. According to one aspect of this invention, this
27 stimulation is administered to the myocardium in order to enhance myocardial function.
28 According to a further aspect of this invention, this stimulation is administered to the cardiac
29 blood pool. This enables cardiac stimulation without the necessity of placing electrical leads in
30 intimate contact with cardiac tissue. According to a still further aspect of this invention, the
31 stimulation is administered to striated muscle tissue to evoke muscular response.

32 The method and apparatus of the present invention comprises a first and second
33 stimulation phase, with each stimulation phase having a polarity, amplitude, shape and duration.

1 in a preferred embodiment the first and second phases have differing polarities. In one
2 alternative embodiment the two phases are of differing amplitude. In a second alternative
3 embodiment the two phases are of differing duration. In a third alternative embodiment the first
4 phase is in a chopped wave form. In a fourth alternative embodiment the amplitude of the first
5 phase is ramped. In a fifth alternative embodiment the first phase is administered over 200
6 milliseconds post heart beat; i.e., greater than 200 milliseconds after the completion of a cardiac
7 beating/pumping cycle. In a preferred alternative embodiment the first phase of stimulation is an
8 anodal pulse at maximum subthreshold amplitude for a long duration, and the second phase of
9 stimulation is a cathodal pulse of short duration and high amplitude. It is noted that the
10 aforementioned alternative embodiments can be combined in differing fashions. It is also noted
11 that these alternative embodiments are intended to be presented by way of example only, and are
12 not limiting.

13 Pacemaker electronics needed to practice the method of the present invention are well
14 known to those skilled in the art. Current pacemaker electronics are capable of being
15 programmed to deliver a variety of pulses, including those disclosed herein.

16 BRIEF DESCRIPTION OF THE DRAWINGS

17 Fig. 1 is a schematic representation of leading anodal biphasic stimulation.

18 Fig. 2 is a schematic representation of leading cathodal biphasic stimulation.

19 Fig. 3 is a schematic representation of leading anodal stimulation of low level and long duration,
20 followed by conventional cathodal stimulation.

21 Fig. 4 is a schematic representation of leading anodal stimulation of ramped low level and long
22 duration, followed by conventional cathodal stimulation.

23 Fig. 5 is a schematic representation of leading anodal stimulation of low level and short duration
24 administered in series, followed by conventional cathodal stimulation.

25 Fig. 6 graphs conduction velocity transverse to the fiber vs pacing duration resulting from
26 leading anodal biphasic pulse.

27 Fig. 7 graphs conduction velocity parallel to the fiber vs pacing duration resulting from leading
28 anodal biphasic pulse.

29 DETAILED DESCRIPTION

30 The present invention relates to the biphasic electrical stimulation of muscle tissue.
31 Figure 1 depicts biphasic electrical stimulation wherein a first stimulation phase comprising
32 anodal stimulus 102 is administered having amplitude 104 and duration 106. This first

1 stimulation phase is immediately followed by a second stimulation phase comprising cathodal
2 stimulation 108 of equal intensity and duration.

3 Figure 2 depicts biphasic electrical stimulation wherein a first stimulation phase
4 comprising cathodal stimulation 202 having amplitude 204 and duration 206 is administered.
5 This first stimulation phase is immediately followed by a second stimulation phase comprising
6 anodal stimulation 208 of equal intensity and duration.

7 Figure 3 depicts a preferred embodiment of the present invention, wherein a first
8 stimulation phase comprising low level, long duration anodal stimulation 302 having amplitude
9 304 and duration 306 is administered. This first stimulation phase is immediately followed by a
10 second stimulation phase comprising cathodal stimulation 308 of conventional intensity and
11 duration. In an alternative embodiment of the invention, anodal stimulation 302 is at maximum
12 subthreshold amplitude. In yet another alternative embodiment of the invention, anodal
13 stimulation 302 is less than three volts. In another alternative embodiment of the invention,
14 anodal stimulation 302 is a duration of approximately two to eight milliseconds. In yet another
15 alternative embodiment of the invention, cathodal stimulation 308 is of a short duration. In
16 another alternative embodiment of the invention, cathodal stimulation 308 is approximately 0.3
17 to 0.8 milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation
18 308 is of a high amplitude. In another alternative embodiment of the invention, cathodal
19 stimulation 308 is in the approximate range of three to twenty volts. In yet another alternative
20 embodiment of the present invention, cathodal stimulation 308 is of a duration less than 0.3
21 milliseconds and at a voltage greater than twenty volts. In another alternative embodiment,
22 anodal stimulation 302 is administered over 200 milliseconds post heart beat. In the manner
23 disclosed by these embodiments, as well as those alterations and modifications which may
24 become obvious upon the reading of this specification, a maximum membrane potential without
25 activation is achieved in the first phase of stimulation.

26 Figure 4 depicts an alternative preferred embodiment of the present invention, wherein a
27 first stimulation phase comprising anodal stimulation 402 is administered over period 404 with
28 rising intensity level 406. The ramp of rising intensity level 406 may be linear or non-linear, the
29 slope may vary. This anodal stimulation is immediately followed by a second stimulation phase
30 comprising cathodal stimulation 408 of conventional intensity and duration. In an alternative
31 embodiment of the invention, anodal stimulation 402 rises to a maximum subthreshold
32 amplitude. In yet another alternative embodiment of the invention, anodal stimulation 402 rises
33 to a maximum amplitude that is less than three volts. In another alternative embodiment of the

invention, anodal stimulation 402 is a duration of approximately two to eight milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation 408 is of a short duration. In another alternative embodiment of the invention, cathodal stimulation 408 is approximately 0.3 to 0.8 milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation 408 is of a high amplitude. In another alternative embodiment of the invention, cathodal stimulation 408 is in the approximate range of three to twenty volts. In yet another alternative embodiment of the present invention, cathodal stimulation 408 is of a duration less than 0.3 milliseconds and at a voltage greater than twenty volts. In another alternative embodiment, anodal stimulation 402 is administered over 200 milliseconds post heart beat. In the manner disclosed by these embodiments, as well as those alterations and modifications which may become obvious upon the reading of this specification, a maximum membrane potential without activation is achieved in the first phase of stimulation.

Figure 5 depicts biphasic electrical stimulation wherein a first stimulation phase comprising series 502 of anodal pulses is administered at amplitude 504. In one embodiment rest period 506 is of equal duration to stimulation period 508, and is administered at baseline amplitude. In an alternative embodiment rest period 506 is of a differing duration than stimulation period 508 and is administered at baseline amplitude. Rest period 506 occurs after each stimulation period 508 with the exception that a second stimulation phase comprising cathodal stimulation 510 of conventional intensity and duration immediately follows the completion of series 502. In an alternative embodiment of the invention, the total charge transferred through series 502 of anodal stimulation is at the maximum subthreshold level. In yet another alternative embodiment of the invention, the first stimulation pulse of series 502 is administered over 200 milliseconds post heart beat. In another alternative embodiment of the invention, cathodal stimulation 510 is of a short duration. In yet another alternative embodiment of the invention, cathodal stimulation 510 is approximately 0.3 to 0.8 milliseconds. In another alternative embodiment of the invention, cathodal stimulation 510 is of a high amplitude. In yet another alternative embodiment of the invention, cathodal stimulation 510 is in the approximate range of three to twenty volts. In another alternative embodiment of the invention, cathodal stimulation 510 is of a duration less than 0.3 milliseconds and at a voltage greater than twenty volts.

EXAMPLE 1

Stimulation and propagation characteristics of the myocardium were studied in isolated hearts using pulses of differing polarities and phases. The experiments were carried out in five

isolated Langendorff perfused rabbit hearts. Conduction velocity on the epicardium was measured using an array of bipolar electrodes. Measurements were made between six millimeters and nine millimeters from the stimulation site. Transmembrane potential was recorded using a floating intracellular microelectrode. The following protocols were examined: monophasic cathodal pulse, monophasic anodal pulse, leading cathodal biphasic pulse and leading anodal biphasic pulse.

Table 1 discloses the conduction speed transverse to fiber direction for each stimulation protocol administered, with stimulations of three, four and five volts and two millisecond pulse duration.

TABLE 1

	Conduction Speed Transverse to Fiber Direction, 2 msec duration		
	3 V	4 V	5 V
Cathodal Monophasic	18.9 ± 2.5 cm/sec	21.4 ± 2.6 cm/sec	23.3 ± 3.0 cm/sec
Anodal Monophasic	24.0 ± 2.3 cm/sec	27.5 ± 2.1 cm/sec	31.3 ± 1.7 cm/sec
Leading Cathodal Biphasic	27.1 ± 1.2 cm/sec	28.2 ± 2.3 cm/sec	27.5 ± 1.8 cm/sec
Leading Anodal Biphasic	26.8 ± 2.1 cm/sec	28.5 ± 0.7 cm/sec	29.7 ± 1.8 cm/sec

Table 2 discloses the conduction speed along fiber direction for each stimulation protocol administered, with stimulations of three, four and five volts and two millisecond pulse duration.

TABLE 2

	Conduction Speed Along Fiber Direction, 2 msec stimulation		
	3 V	4 V	5 V
Cathodal Monophasic	45.3 ± 0.9 cm/sec	47.4 ± 1.8 cm/sec	49.7 ± 1.5 cm/sec
Anodal Monophasic	48.1 ± 1.2 cm/sec	51.8 ± 0.5 cm/sec	54.9 ± 0.7 cm/sec
Leading Cathodal Biphasic	50.8 ± 0.9 cm/sec	52.6 ± 1.1 cm/sec	52.8 ± 1.7 cm/sec
Leading Anodal Biphasic	52.6 ± 2.5 cm/sec	55.3 ± 1.5 cm/sec	54.2 ± 2.3 cm/sec

The differences in conduction velocities between the cathodal monophasic, anodal monophasic, leading cathodal biphasic and leading anodal biphasic were found to be significant ($p < 0.001$). From the transmembrane potential measurements, the maximum upstroke ($(dV/dt)_{max}$) of the action potentials was found to correlate well with the changes in conduction velocity in the longitudinal direction. For a four volt pulse of two millisecond duration, $(dV/dt)_{max}$ was 63.5 ± 2.4 V/sec for cathodal and 75.5 ± 5.6 V/sec for anodal pulses.

EXAMPLE 2

The effects of varying pacing protocols on the cardiac electrophysiology were analyzed using Langendorff prepared isolated rabbit hearts. Stimulation was applied to the heart at a constant voltage rectangular pulse. The following protocols were examined: monophasic anodal pulse, monophasic cathodal pulse, leading anodal biphasic pulse and leading cathodal biphasic pulse. Administered voltage was increased in one volt steps from one to five volts for both anodal and cathodal stimulation. Duration was increased in two millisecond steps from two to ten milliseconds. Epicardial conduction velocities were measured along and transverse to the left ventricular fiber direction at a distance between three to six millimeters from the left ventricular free wall. Figures 6 and 7 depict the effects of stimulation pulse duration and the protocol of stimulation administered on the conduction velocities.

Figure 6 depicts the velocities measured between three millimeters and six millimeters transverse to the fiber direction. In this region, cathodal monophasic stimulation 602 demonstrates the slowest conduction velocity for each stimulation pulse duration tested. This is followed by anodal monophasic stimulation 604 and leading cathodal biphasic stimulation 606. The fastest conduction velocity is demonstrated by leading anodal biphasic stimulation 608.

Figure 7 depicts the velocities measured between three millimeters and six millimeters parallel to the fiber direction. In this region, cathodal monophasic stimulation 702 demonstrates the slowest conduction velocity for each stimulation pulse duration tested. Velocity results of anodal monophasic stimulation 704 and leading cathodal biphasic stimulation 706 are similar, with anodal monophasic stimulation demonstrating slightly quicker speeds. The fastest conductive velocity is demonstrated by leading anodal biphasic stimulation 708.

In one aspect of the invention, electrical stimulation is administered to the cardiac muscle. The anodal stimulation component of biphasic electrical stimulation augments cardiac contractility by hyperpolarizing the tissue prior to excitation, leading to faster impulse conduction, more intracellular calcium release, and the resulting superior cardiac contraction. The cathodal stimulation component eliminates the drawbacks of anodal stimulation, resulting in effective cardiac stimulation at a lower voltage level than would be required with anodal stimulation alone. This in turn, extends pacemaker battery life and reduces tissue damage.

In a second aspect of the invention, biphasic electrical stimulation is administered to the cardiac blood pool, that is, the blood entering and surrounding the heart. This enables cardiac stimulation without the necessity of placing electrical leads in intimate contact with cardiac tissue.

1 In a third aspect of the invention, biphasic electrical stimulation is applied to striated
2 muscle tissue. The combination of anodal with cathodal stimulation results in the contraction of
3 a greater number of muscular motor units at a lower voltage level, resulting in improved
4 muscular response.

5 Having thus described the basic concept of the invention, it will be readily apparent to
6 those skilled in the art that the foregoing detailed disclosure is intended to be presented by way of
7 example only, and is not limiting. Various alterations, improvements and modifications will
8 occur and are intended to those skilled in the art, but are not expressly stated herein. These
9 modifications, alterations and improvements are intended to be suggested hereby, and within the
10 spirit and scope of the invention. Further, the pacing pulses described in this specification are
11 well within the capabilities of existing pacemaker electronics with appropriate programming.
12 Accordingly, the invention is limited only by the following claims and equivalents thereto.

1 What is claimed is:

2 1. A method for biphasic electrical cardiac pacing comprising.

3 defining a first stimulation phase with a first phase polarity, a first phase amplitude, a first
4 phase shape and a first phase duration for preconditioning the myocardium to accept subsequent
5 stimulation;

6 defining a second stimulation phase with a polarity opposite to the first phase polarity, a
7 second phase amplitude that is larger in absolute value than the first phase amplitude, a second
8 phase shape and a second phase duration; and

9 applying the first stimulation phase and the second stimulation phase in sequence to
10 cardiac tissue.

11 2. The method for biphasic electrical cardiac pacing of claim 1 wherein the first phase
12 polarity is positive.

13 3. The method for biphasic electrical cardiac pacing of claim 1 wherein the first phase
14 amplitude is ramped from a baseline value to a second value.

15 4. The method for biphasic electrical cardiac pacing of claim 1 wherein the first
16 stimulation phase further comprises a series of stimulating pulses of a predetermined amplitude,
17 polarity and duration.

18 5. The method for biphasic electrical cardiac pacing of claim 4 wherein the first
19 stimulation phase further comprises a series of rest periods.

20 6. The method for biphasic electrical cardiac pacing of claim 5 wherein applying the first
21 stimulation phase further comprises applying a rest period of a baseline amplitude after at least
22 one stimulating pulse.

23 7. The method for biphasic electrical cardiac pacing of claim 6 wherein the rest period is
24 of equal duration to the stimulating pulse.

25 8. The method for biphasic electrical cardiac pacing of claim 1 wherein the first phase
26 amplitude is at a maximum subthreshold amplitude.

27 9. The method for biphasic electrical cardiac pacing of claim 8 wherein the maximum
28 subthreshold amplitude is about 0.5 to 3.5 volts.

29 10. The method for biphasic electrical cardiac pacing of claim 1 wherein the first phase
30 duration is at least as long as the second phase duration.

31 11. The method for biphasic electrical cardiac pacing of claim 1 wherein the first phase
32 duration is about one to nine milliseconds.

1 12. The method for biphasic electrical cardiac pacing of claim 1 wherein the second
2 phase duration is about 0.2 to 0.9 milliseconds.

3 13. The method for biphasic electrical cardiac pacing of claim 1 wherein the second
4 phase amplitude is about two volts to twenty volts.

5 14. The method for biphasic electrical cardiac pacing of claim 1 wherein the second
6 phase duration is less than 0.3 milliseconds and the second phase amplitude is greater than 20
7 volts.

8 15. The method for biphasic electrical cardiac pacing of claim 3 wherein the second
9 value is at a maximum subthreshold amplitude.

10 16. The method for biphasic electrical cardiac pacing of claim 15 wherein the maximum
11 subthreshold amplitude is about 0.5 to 3.5 volts.

12 17. The method for biphasic electrical cardiac pacing of claim 3 wherein the first phase
13 duration is at least as long as the second phase duration.

14 18. The method for biphasic electrical cardiac pacing of claim 3 wherein the first phase
15 duration is about one to nine milliseconds.

16 19. The method for biphasic electrical cardiac pacing of claim 3 wherein the second
17 phase duration is about 0.2 to 0.9 milliseconds.

18 20. The method for biphasic electrical cardiac pacing of claim 3 wherein the second
19 phase amplitude is about two volts to twenty volts.

20 21. The method for biphasic electrical cardiac pacing of claim 3 wherein the second
21 phase duration is less than 0.3 milliseconds and the second phase amplitude is greater than 20
22 volts.

23 22. The method for biphasic electrical cardiac pacing of claim 1 wherein the first
24 stimulation phase is initiated greater than 200 milliseconds after completion of a cardiac beating
25 cycle.

26 23. A method for biphasic electrical cardiac pacing comprising:
27 initiating the application of a first stimulation phase for preconditioning the myocardium,
28 wherein the first stimulation phase comprises:

29 a positive polarity;

30 a first phase amplitude;

31 a first phase shape; and

32 a first phase duration, wherein said first phase amplitude is about 0.5 to 3.5 volts,

33 wherein said first phase duration is about one to nine milliseconds and wherein said first

1 stimulation phase is initiated greater than 200 milliseconds after completion of a cardiac beating
2 cycle;

3 initiating the application of a second stimulation phase, wherein the second stimulation
4 phase comprises:

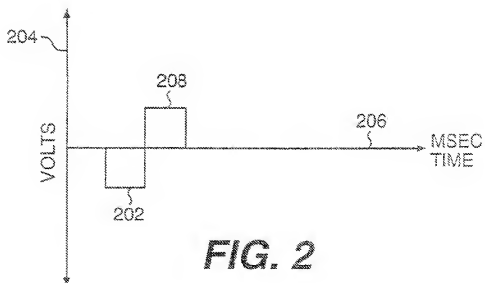
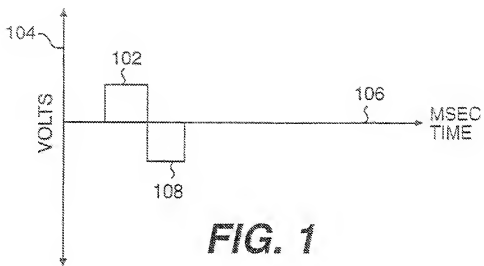
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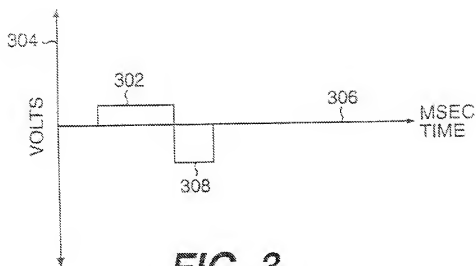
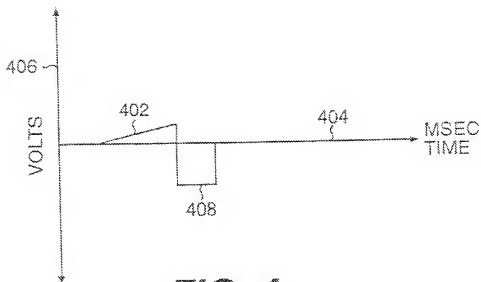
6 a second phase amplitude;

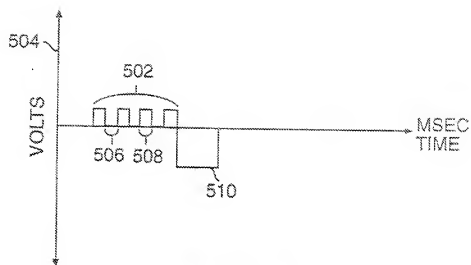
7 a second phase shape; and

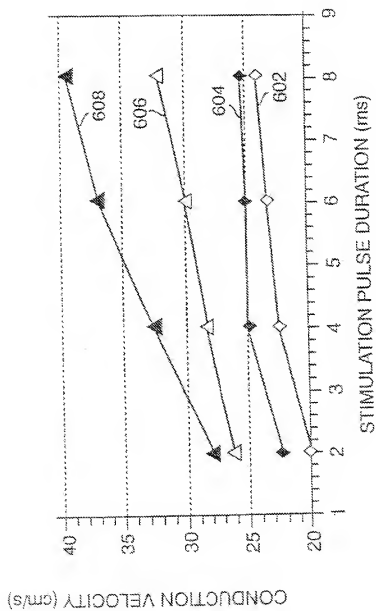
8 a second phase duration, wherein said second phase amplitude is about four volts
9 to twenty volts and wherein said second phase duration is about 0.2 to 0.9 milliseconds; and

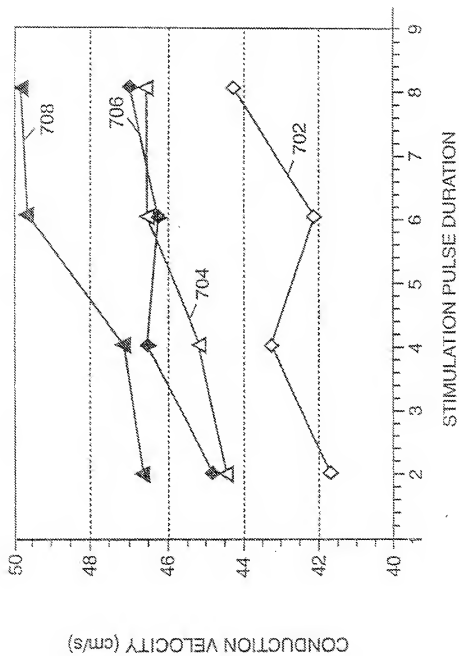
10 applying the first stimulation phase and the second stimulation phase in sequence to
11 cardiac tissue.



**FIG. 3****FIG. 4**

**FIG. 5**

**FIG. 6**

**FIG. 7**

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 98/13737

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/362

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 343 312 A (CALS GUILLAUME L M ET AL) 10 August 1982 cited in the application see column 4, line 28-60 see column 6, line 15 - column 7, line 34; figures 2B, 3B, 3C	1
X	US 4 903 700 A (WHIGHAM ROBERT H ET AL) 27 February 1990 cited in the application see column 5, line 21-47 see column 6, line 7-64 see column 15, line 66 - column 16, line 12; figure 4	1

-/-

☒ Further documents were listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of prior documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published only after the international filing date
- "L" document which may throw doubts on priority (claims) or which is cited to establish the publication date of another claim or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "S" document member of the same patent family

Date of the closest completion of the international search

27 January 1999

Date of mailing of the international search report

03/02/1999

Name and mailing address of the ISA

European Patent Office P.O. Box 588 Patankas 2
D-69110 Heidelberg
Germany

Authorized officer

INTERNATIONAL SEARCH REPORT

In International Application No.

PCT/US 98/13737

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 543 956 A (HERSCOVICI HARRY) 1 October 1985 cited in the application see column 2, line 61 - column 3, line 45; figure 1 -----	1
A	US 5 601 608 A (MOUCHAWAR GABRIEL) 11 February 1997 see column 2, line 3-37 see column 7, line 59 - column 8, line 14 see column 10, line 63 - column 11, line 10; figures 5,7,9,11 -----	1
A	US 4 402 322 A (DUGGAN STEPHEN R) 6 September 1983 see column 2, line 17-24; figure 3 -----	1
A	EP 0 491 649 A (VENTRITEX INC) 24 June 1992 see column 2, line 42 - column 3, line 57; figures 1,2 -----	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although the claims are directed to a method of treatment of the human/animal body, the search has been carried out based a device capable of carrying out the method of claim 1.

Claims Nos.: 1-23

Rule 39.1(iv) PCT -- Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on parent family members

In: International Application No.

PCT/US 98/13737

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